REMARKS

Claims 1-2 and 4-11 were pending. Claims 2 and 4-11 were amended for clarity without prejudice and without acquiescence. No new matter is entered herein.

I. Issue Under 35 USC 112, first paragraph; Enablement

Claims 1-2 and 4-11 were rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully disagree.

In particular, the Examiner rejects claims 1-2 and 4-11 as lacking enablement because the specification allegedly fails to provide sufficient guidance concerning:

1. how the presence of an elevated level of ADMA can be used to determine whether or not a pregnant woman is at risk of developing pre-eclampsia or her fetus is at risk of developing intrauterine growth restriction (IUGR); and

2. how the method can be practiced in any sample taken from the woman.

Applicants traverse and assert that, based on the information provided in the instant specification, a person skilled in the art is able to practice the claimed invention. For the reasons discussed below, measuring a level of ADMA of greater than 2.0 μmol/L in any sample from a woman is a good marker for whether or not the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR, as claimed.

We address each of issues 1 and 2 below and provide copies of the noted documents in a Supplemental Information Disclosure Statement filed herewith.

Issue 1

Pre-eclampsia is a multifactorial disease

In raising the rejection of lack of enablement, the Examiner cites on page 5 of the Office Action various documents that are characterized by the Examiner as disclosing that:

(a) the level of ADMA correlates with traditional and non-traditional cardiovascular risk factors (Cooke);

(b) ADMA is a strong predictor of cardiovascular events and deaths in selected patient populations (Kielstein *et al.*);

(c) ADMA is a marker of progression of various chronic renal diseases (Kielstein *et al.*);

(d) high ADMA levels have been associated with alterations in the regulation of cerebral blood flow and neural function, with insulin resistance, thyroid dysfunction, alterations in bone homeostasis, fertility and erectile function (Kielstein *et al.*); and

(e) higher levels of ADMA have been observed in onset of menopause, smoking, infection, high salt intake and fatty food intake (Fang *et al.*, Fard *et al.* and Hamasaki *et al.*).

First, Applicants note that the post-filing date references of Kielstein *et al.* and Fang *et al.* should not be used to demonstrate non-enablement. M.P.E.P. § 2164.05(a). As stated therein,

> In general, the examiner should ***not*** use post-filing date references to demonstrate that the patent is non-enabling. ***Exceptions*** to this rule could occur ***if a later-dated reference provides evidence of what one skilled in the art would have known*** on or before the effective filing date of the patent application. *In re Hogan*, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977) (emphasis added).

These particular references relied upon in the Action to support non-enablement are dated after Applicants' filing date of April 19, 2004, and they do not fall under the exceptions to this rule because they fail to provide evidence of what the skilled artisan would have known at the time of filing. That is, Kielstein *et al.* concerns ADMA and its association with cardiovascular complications and renal diseases, which says nothing about the efficacy of ADMA for identifying a woman at risk for pre-eclampsia or fetal risk for IUGR. Furthermore, Fang *et al.* concerns ADMA modulation by chronic salt loading in normotensive salt-sensitive individuals, which does not preclude the enablement for using ADMA levels for Applicants' purpose. Both references say nothing about whether or not one could or could not ascertain the amount of ADMA to identify whether or not a pregnant

woman is at risk of developing pre-eclampsia or whether or not her fetus is at risk of developing IUGR. They also fail to provide a sufficient reason to doubt enablement. M.P.E.P. § 2164.04. Therefore, it is improper to employ these references in the Examiner argument's arguments.

Nevertheless, Applicants address all of the references on their merits. Based on this art, the Examiner takes the view that ADMA could be modulated in pregnant women by other disorders and therefore cannot be relied upon as a marker for risk of pre-eclampsia or IUGR. However, it should be noted that pre-eclampsia is a complex, multifactorial disease involving changes in many organ systems. For instance, changes in blood pressure, platelet aggregation, liver function, and renal function are typical indices of the disease. More specifically, many of the diseases and conditions referred to by the Examiner on page 5 of the Office Action are associated with pre-eclampsia. For example, Bellamy *et al.* disclose a close association between pre-eclampsia and cardiovascular disease and even suggested a common cause.

It is also known from clinical practice that failure to treat pre-eclampsia effectively, such that eclampsia develops, can lead to neurological symptoms, such as fits. Furthermore, intra-cerebral haemorrhage has been observed as a complication of pre-eclampsia (see, for example, Dai and Diamond). Abnormal metabolic states, such as insulin resistance, are also known to be present during pregnancy and exacerbated in pre-eclampsia (Damm *et al.*). Abnormalities in thyroid function have also been observed in pre-eclampsia (Kumar *et al.*), as have changes in bone metabolism (Shaarawy *et al.*). Boomsma *et al.* have also found an association between polycystic ovary syndrome, a known factor in infertility, and pre-eclampsia.

Altered ADMA due to menopause is unlikely to be a confounding factor in pregnancy. However, pregnancies in menopausal women are often associated with similar complications to non-menopausal women and recommendations including close obstetric monitoring (Antinori *et al.*). The fact that high ADMA levels have been associated with erectile dysfunction is irrelevant when considering the enablement of the claimed methods, which involve measuring ADMA in a pregnant woman. It is therefore clear that many, if not all, of the conditions cited by the Examiner on page 5 of the Office Action are associated with

pre-eclampsia in pregnant woman. Hence, it is hardly surprising that changes in ADMA are observed in those conditions, even in the absence of pre-eclampsia, since the underlying pathologies may be the same or similar.

However, that does not mean that elevated ADMA is not an effective marker for the risk of developing pre-eclampsia or IUGR. If anything, the art cited by the Examiner supports the teaching of the instant specification. As clearly shown in the Examples, an elevated ADMA level early in pregnancy is a clear indicator that a pregnant woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR. In other words, an elevated ADMA level early in pregnancy is a clear indicator that a pregnant woman is at risk of developing during pregnancy a complex, multifactorial disease involving changes in, amongst others, her cardiovascular function, metabolic function and renal function. To put it another way, the art cited by the Examiner does not teach that ADMA could be modulated in pregnant women by other disorders and therefore cannot be relied upon as a marker for risk of pre-eclampsia or IUGR. Instead, it teaches that ADMA is a good marker for the risk of pre-eclampsia, because alterations in its level are observed in many conditions that in pregnant women may develop into the complex disease named pre-eclampsia. The clinical definition of pre-eclampsia is discussed in more detail below.

Elevated ADMA in pre-eclampsia

On page 6 of the Office Action, the Examiner cites a document by López-Jamarillo *et al.* and references cited therein. Based on these references, the Examiner concludes that ADMA is not elevated in pre-eclampsia and suggests that the cause of pre-eclampsia differs amongst disparate ethnic and geographic groups.

For a start, in making this conclusion, the Examiner seems to have ignored the disclosure of other documents that he himself has cited. For instance, Holden *et al.* conclude that there is a difference in ADMA concentrations between pre-eclamptic and non-pre-eclamptic patients in the third trimester of pregnancy (see abstract). Similarly, Cooke discloses that ADMA levels are elevated in pre-eclampsia (first full paragraph in the left-hand column on page 1814). Indeed, Cooke confirms the result disclosed in the instant specification, namely that the elevation of plasma ADMA occurs before any clinical evidence

of pre-eclampsia. In addition, although López-Jamarillo *et al.* report no differences in plasma ADMA between pre-eclampsia and non-pre-eclampsia patients and amongst different ethnic groups, they were unable to offer any explanation for this observation.

Based on the results presented, the Examiner states on page 6 of the Office Action that "López-Jamarillo concludes that the etiologic process that leads to a vascular endothelial dysfunction are different between populations from developed and developing countries" and that "while the immunological and genetic alterations are relevant in the development of pre-eclampsia in developed countries, nutritional, metabolic and infectious factors are the major responsible for the high incidence of pre-eclampsia seen in developing countries". This leads the Examiner to conclude that measuring ADMA cannot provide any reliable information concerning the risk of developing pre-eclampsia in different populations.

Applicants disagree. To their knowledge, there is no widely accepted model as to the cause of pre-eclampsia. There are several well-described pathological features of pre-eclampsia, in particular poor implantation and development of the placenta. This has lead to the theory that an improperly developed placenta can lead to placental distress, which contributes to the development of pre-eclampsia. In other words, immunological or genetic alterations are likely to be responsible for pre-eclampsia in all populations and not just patients from developed countries as the Examiner suggests.

However, it is also recognized that certain factors increase the risk of developing pre-eclampsia. Such factors include elevated blood pressure, insulin resistance or diabetes, obesity, nutritional status, previous pre-eclampsia and familial history. Given this, the Examiner's conclusion that nutritional, metabolic and infectious factors are the cause of pre-eclampsia in developing countries is incorrect. Nutritional, metabolic and infectious factors merely increase the likelihood that pregnant women in developing countries will display symptoms of pre-eclampsia.

While López-Jamarillo *et al.* found that treatment of infections in pregnancy led to a reduction in development of pre-eclampsia, this was secondary to calcium and fatty supplementation. A recent meta-analysis of the association between infection and pre-eclampsia by Conde-Agudelo *et al.* found that the risk of developing pre-eclampsia was

increased in pregnant women with urinary tract infection and periodontal disease, but not with many other infectious diseases including bacterial vaginosis. Thus, it is not correct to claim that infectious diseases, which may differ amongst different populations, are causative of pre-eclampsia. Instead, it is only viable to claim that in some instances infectious diseases increase the risk of developing pre-eclampsia.

The cause and progression of pre-eclampsia will be similar, if not the same, in developed and developing countries. Given this, as discussed below, an elevated ADMA level in a pregnant woman from any population before any clinical symptoms of pre-eclampsia are observed is a good indicator that the woman is susceptible to pre-eclampsia.

ADMA as a predictor of the risk of developing of pre-eclampsia

The Examiner cites the document by Holden *et al.* as anticipating the use of ADMA to predict the risk of developing pre-eclampsia and also cites the document by López-Jamarillo *et al.* as teaching against an elevated level of ADMA in pre-eclampsia.

As disclosed in the abstract of the document by Holden *et al.*, the level of ADMA in a pregnant woman falls in early pregnancy, but rises later in pregnancy as blood pressure rises. Some studies do not find any difference in the ADMA level in pre-eclamptic and non-pre-eclamptic women near term (López-Jamarillo *et al.*), whereas others do (Holden *et al.*). Perhaps the normal rise in ADMA towards the end of pregnancy masked any difference between the non-pre-eclamptic and pre-eclamptic patients in the study by López-Jamarillo *et al.*

In any case, the key point is that the current claims are not directed to diagnosing pre-eclamapsia. The current claims are directed to identifying whether or not a pregnant woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR.

All of the studies cited by the Examiner compare ADMA levels in patients with and without pre-eclampsia in the third trimester. In other words, the studies compare a group of patients that have already been diagnosed with pre-eclampsia with a group of patients that do not have pre-eclampsia and are at the same stage of pregnancy.

As a result, the studies are irrelevant when considering whether elevated ADMA in earlier pregnancy is a good predictor of the likelihood of a woman developing pre-eclampsia. None of these studies were designed to determine the usefulness of ADMA as a predictor of whether or not a woman in early pregnancy (without pre-eclampsia) is likely to develop pre-eclampsia later in pregnancy. In particular, none of the studies measure ADMA early in pregnancy in women with no clinical symptoms of pre-eclampsia. In addition, none of the studies correlate early ADMA levels with the subsequent development of pre-eclampsia later in pregnancy.

Given this, the level of ADMA in women with or without pre-eclampsia and in the third trimester of pregnancy (as reported by Holden *et al.* and López-Jamarillo et al .) has no bearing on whether or not ADMA make be used early in pregnancy as a predictor of the risk of developing pre-eclampsia. The instant specification clearly demonstrates that ADMA can be used early in pregnancy, such as from 10 to 25 weeks of gestation, for example, as an indicator of whether or not a pregnant woman will develop pre-eclampsia later in pregnancy. It is this disclosure that enables a person skilled in the art to perform the claimed methods.

The Examiner has not provided any evidence to contradict the disclosure in the instant specification. In particular, the Examiner has not provided any evidence that an elevated ADMA level early in pregnancy cannot be used to predict the likelihood of developing pre-eclampsia later in pregnancy.

Issue 2

The instant specification provides sufficient information to allow a person skilled in the art to carry out the claimed method using any sample from a pregnant woman. The specification at least at paragraphs **[0031]** and **[0085]** describe exemplary samples that may be utilized. The Examples clearly show that the level of plasma ADMA in a pregnant woman is indicative of whether or not the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR. The concentration ADMA is homogenous throughout the body. As a result, it is expected that the concentration of ADMA is the same in any tissue or fluid sample taken from a pregnant woman. The Examiner has provided no evidence to contradict this.

In raising the rejection of lack of enablement, the Examiner cites a document by Cobb *et al.* As the Examiner correctly indicates, Cobb *et al.* teaches that sepsis induces the expression of different genes to differing extents in mouse spleen compared with mouse liver. However, we fail to see how this is relevant to the use of the level of ADMA as a marker for the risk of developing pre-eclampsia. The document by Cobb *et al.* measures the expression of various genes and not the actual concentration of ADMA in different tissues.

It is well known that different tissues express genes to differing extents. However, this does not mean that the level of a circulating biomarker will differ between different tissues. ADMA is an endogenous inhibitor of nitric oxide synthase that is produced by protein methyltransferases (paragraph **[0004]** on page 2 of the instant specification). It is expected that the level of ADMA will be the same throughout all the fluids and tissues of a pregnant woman. As a result, any sample from a pregnant woman may be used in the claimed methods.

Applicants submit that the level of ADMA in a pregnant woman can be used to predict whether or not a pregnant woman will develop pre-eclampsia or her fetus will develop IUGR. The instant specification provides sufficient information to enable a person skilled in the art to carry out the claimed methods across their entire scope. Applicants respectfully request withdrawal of the rejection.

II. Issue Under 35 USC 112, second paragraph

Claims 1-2 and 4-11 were rejected under 35 USC 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants respectfully disagree.

A. Claim 1

On page 9 of the Office Action, the Examiner rejects claim 1 as being indefinite because allegedly it "does not recite a positive step linking the preamble to the claimed method". The Examiner also states that claim 1 merely recites "determining whether or not the level is 2.0μmol/L without positive delineating what ADMA level of more or less than 2.0μmol/L would actually mean to the method claimed".

Applicants submit that claim 1 is perfectly clear to a person skilled in the art. The claim explicitly states that the method of the invention involves "*determining whether or not the ADMA is greater than 2.0 μmol/L in the woman, thereby determining whether or not the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR*" (emphasis added). A person skilled in the art reading the claim in isolation or in the context of the instant specification as a whole would clearly understand that an ADMA level of greater than 2.0 μmol/L in a woman is indicative of the woman being at risk of developing pre-eclampsia or her fetus being at risk of developing IUGR.

Applicants respectfully request withdrawal of the rejection.

B. Claims 2 and 4 to 11

Applicants have amended all of the dependent claims as the Examiner requested. Applicants respectfully request withdrawal of the rejection.

III. Issue Under 35 USC 102(b)

Claims 1-2, 4, and 5 were rejected under 35 USC 102(b) as allegedly being anticipated by Holden *et al.* (Am. J. Obstet. Gynecol. 1998:178(3):551-6; "Holden"). Applicants respectfully disagree.

The Examiner rejects claims 1-2 and 4-5 as lacking novelty in view of Holden *et al.* As discussed above, claim 1 is limited to a method in which a level of ADMA of greater than 2.0μmol/L is indicative of the woman being susceptible to pre-eclampsia. The document by Holden *et al.* does not disclose such a method. As can be seen from Figure 1B on page 553, the study by Holden *et al.* only measured plasma ADMA concentrations up to 1.25μmol/L.

Applicants therefore submit that all of the claims are novel and respectfully request withdrawal of the rejection.

IV. Conclusion

Applicants believe no fees are due other than the fee for the Petition for Extension of Time of Three Months and the Supplemental Information Disclosure Statement. However,

the Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 06-2375, under Order No. HO-P03236US0.

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